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10/617,888	07/14/2003	Donald Jeffery Zack	01107.00369	3409

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EXAMINER

LEAVITT, MARIA GOMEZ

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/617,888		ZACK ET AL.	
	Examiner		Art Unit	
	Maria Leavitt		1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-53 is/are pending in the application.
- 4a) Of the above claim(s) 1-9, 11 and 20-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10 and 12-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Applicant's election of Group II (claims 10, 12-19) in the reply filed on 02-21-2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

With regard to restriction requirements, Applicant election of species is acknowledged for the following specie: MN androgen marker as neuronal marker. Applicant's election of the following specie, retinal cell degeneration, does not correspond to any of the species as recited by the Examiner on pp. 9 and 10 a-h, in the requirements for restriction of 11-02-2005. The examiner has interpreted the elected specie as age-related macular degeneration, as recited in p. 10, h.

Claims 1-9, 11, and 20-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention.

Currently, claims 10, 12-19 are pending to which the following grounds of rejection are applicable.

Drawings Objection

The drawings are objected to under 37 CFR 1.83(a) because the specification discloses a list of genes and they are referred to in the specification as Figures (e.g., p. 46, EXAMPLES [50] and [51]). Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second paragraph-

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, and 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 (and dependent claims) is indefinite in its recitation of “preventing” since it is unclear how this term is defined, what its metes and bounds are, or to what the term is directed towards. It is not clear whether preventing refers to prevention of quiescent stages of cell death, which persists below the threshold in most cells, or the eminent cell death as a result of diverse activating stimuli (Davis, 2001, Curr Opin Investig Drugs. 2001, p. 654, col. 2, last paragraph)

Claims 10, and dependent claims 12-19 are rejected under 35 U.S.C. 112. Claim 10 recites the limitation "inhibited" on p. 53, first paragraph, and last line. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112- First paragraph- Written description

Claims 10 and dependent claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the

application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 10 encompass a genus of unspecified “neuronal markers” for prevention of any neuronal cell death in a mammal. Additionally, claim 10 encompasses a genus of NM androgen binding proteins. The “neuronal markers” when given the broadest reasonable interpretation encompass a genus of unspecified variants of neuronal markers that may prevent neuronal cell death in a treated patient. Additionally, a NM androgen binding protein when given the broadest reasonable interpretation encompass a genus of unspecified polymorphic or allelic variants of a NM androgen binding protein. Applicant discloses in the specification, pp. 2-7 [06] an extensive list of nucleic acid molecules comprising a coding sequence for a neuronal marker. Additionally, the specification discloses that neuronal cell death markers identified herein were identified using available reagents for probes (p. 44 [44]). However, apart from these disclosures, the as-filed specification does not teach how to select or use any of the neuronal cell death markers, nor does it disclose what properties of neuronal cell death markers are desirable for use in the methods of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was “ready for patenting”, or by describing distinguishing identifying characteristics sufficient to

show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant merely provides a list of neuronal cell markers. However, the term “neuronal cell marker” encompasses a genus of species having different chemical structures, physical properties and biological functions. Moreover, the specification does not provide any disclosure as to what would have been the required structure of the claimed genus of any specific markers and/or steps that would have prevent neuronal cell death by using any neuronal marker.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., amino acid sequence), specific features and functional attributes (e.g., how neuronal cell death is prevented) that would distinguish different members of the claimed genus. In the instant case, no other characteristic in

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addition to the functional discussed above is disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of neuronal markers or a genus of polymorphic or allelic variants of a NM androgen binding protein, at the time the application was filed.

Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112- First paragraph-

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 12-19, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make an/or use the invention.

The specification does not reasonably provide enablement for claims directed to a method of preventing neuronal cell death in a mammal comprising administering to said mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease occasioned by neuronal cell death (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders).

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention breadth of the claim

The present invention is drawn to a method of preventing neural cell death by administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease associated with neuronal cell death. Although the specification states, “ nucleic acids and the corresponding encoded

proteins markers of the present invention can be used therapeutically in a variety of modes (p. 45, [46], the specification does not provide any specific and substantial or well-established use comprising administering a nucleic acid molecule expressing a neuronal marker of the elected species invention (e.g., NM androgen binding protein). Therefore, the composition claims 10, 12-19 are interpreted as being drawn non-viral therapeutic preventions.

The claims when given the broadest reasonable interpretation encompass a method of administering a nucleic acid molecule expressing a neuronal marker, by any route, wherein the nucleic acid of the composition can effectively be expressed for the intended use of preventing a disease associated with neuronal cell death.

Specific considerations for *in vivo* gene therapeutic transfer such as *systemic barriers* (e.g., degradation of DNA in plasma, inability of DNA to target specific organs, largely ineffective administration via the oral route) and *cellular DNA barriers* (e.g. endosomal escape of DNA, lysosomal degradation, cytoplasmic stability of DNA, translocation of DNA to the nucleus) have to be addressed for an *in vivo* gene therapy method of preventing a human disorder disease associated with neuronal cell death. Though Applicant's specification discloses in example [50] gene expression using arrays of probes as shown in Figure 9, the broad aspects of gene therapy composition to treat any human disorder having an inflammatory component is not reasonably enable for the full scope embraced by the claims.

The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcome by the as-filed application.

State of the prior art

The Invention is in the nature of a method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease associated with neuronal cell death.

Regarding the claimed invention drawn to a method of administering a composition comprising a nonviral, free DNA vector, for prevention of any type disorder associated by neuronal cell death, Applicant' claims as written encompass a genus of nucleic acid molecules to prevent any human disorder characterized by neuronal cell death. For non-viral gene therapy the specific target of the disease have to be known, since clinical success is empirical and must be determine on a case-by case bases. For example, in the case of an inherited disorder, the insertion of a new gene that ultimately corrects a deficiency requires that the new gene product is present in sufficient amount to achieve a therapy. By contrast, in acquired diseases, since a particular gene or unrelated biochemist process may contribute to the disorder, the approach to therapeutically target a human disorder is complex by the number of factors to be considered and often the incomplete understanding of the pathology of the disease. Besides understanding of how a mutation leads to a disease, it is important to determine which cells of the body are suitable targets for effective therapy, for examples, disorders resulting from the deficiency of a circulating protein (e.g., clotting factors) may be corrected by expression of the relevant gene in skin or muscle cells, even if the protein is normally made in liver, as long as is secreted into the bloodstream (Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995, p10, paragraph 3). Thus, each therapeutic approach should encompass the specifics for the human disorder being contemplated. Hence the

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application of gene transfer technology is complex and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies (see, Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 1996, p.81). Of note, the Marshall reference (*Science*, 1995, 269, pp. 1050-1055,) indicates," there has been no unambiguous evidence that prevention has produced therapeutic benefit (page 1050, column 1). Even data from the pioneering ADA trials are not decisive and "difficulties in getting genes transferred efficiently to target cells, and getting them expressed, remains a nagging problem for the entire field (page 1054, column 3). This problem afflicts all areas of gene therapy (see, p. 1050)." Concurring with Marshall, Verma and Somia (*Nature*, 1997) state that " the Achilles heel of gene therapy is gene delivery... and thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ...[non-viral gene therapy approaches] suffer from poor efficiency of delivery and transient expression of gene" and they go on to say that "although there are reagents that increase the efficient delivery, transient expression of the transgene is a conceptual hurdle that needs to be addressed " (*Nature*, 1997, p. 239, col. 2, paragraph 2). The specification is silent about any specific examples for preventing any disorder associated with neuronal cell death. Hence, it would be undue experimentation for one of ordinary skill in the Art to make and use any type of method to prevent a human disorder associated with neuronal cell death by using a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent said disorder.

In relation to the method of administering composition comprising a nonviral, free DNA vector encoding a gene product comprising a coding sequence for a neuronal marker for the intended use in gene therapy, prior art discloses systemic and intracellular barriers affecting

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expression of non-viral gene expression constructs. For example, problems related to naked DNA digestion by bloodstream nucleases and deposits of large DNA molecules in the first capillary bed encountered after intravenous injection (diverting complexes injected into organs, to enable their circulation) can be reduced by condensing the DNA with polycationic chitosan (Brown MD, *Int J Pharm*, p. 4, col. 2, paragraph 3). Though the Art has developed strategies to overcome extracellular systemic barriers, the Art also recognizes the importance of studying gene therapy in the context of a specific disease since it was found that even gene transfer to the lung epithelium is severely limited by purulent infective sputum, a normal feature of cystic fibrosis lung, and by normal mucus (Brown et al., p. 13, col. 1, paragraph 1). In relation to intracellular barriers, the synthetic gene-transfer complexes face several obstacles to reach the cell nucleus for transcription of the delivered DNA. After internalization by receptor-mediated or adsorptive endocytosis, the complex is enclosed within the endosomal or lysosomal membrane, and therefore separated from the cytoplasm. A combination of both endosomal disrupting peptides and receptor mediated uptake have been used in complexes to facility the endosomal barrier and specific cell uptake, however all these strategies have enjoyed moderated success (Brown, p. 13, col. 1, paragraph 2). The inability to achieve effective gene transfer in differentiated; non-dividing cells possessing an intact nuclear membrane may pose the most important limitation for successful nonviral gene transfer (Zabner et al., *JBC*, 270, 18997-19007, 1995, p. 19005, col. 2, paragraph 1 and 2). Lechardeur et al. described metabolic instability of plasmid DNA in the cytosol as a further barrier to gene transfer (*Gene Ther.* 6:482-497, 1999). Hence, one skilled in the Art at the time of the invention could not reasonably predict the use of any method of administering, by any route, a nucleic acid molecule

expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a disorder associated with neuronal cell death.

Insofar as the prevention of neuronal cell death in a mammal, the claims when given the broadest possible interpretation encompasses any neuronal disease of the nervous system, from neurodegenerative diseases, such as Alzheimer's disease (AD) and stroke, to severe psychosocial trauma (Koliatsos et al., 1999, Cell death and disease of the nervous system, p. 549, paragraph 2). Boxer et al., discloses that mechanisms involved in producing cell death involved activation or blockade of cell-surface receptors and/or intracellular targets. The regulation of extrinsic and intrinsic mechanisms leading to neuronal cell death is present in two distinct pathways, the traditional one of necrotic cell death and a second one, by apoptosis or programmed cell death (PCD) (Boxer et al., 1997, Drug Discovery Today, p. 219, col. 2 and p. 221, Fig. 1).

Regarding activation or blockade of cell surface receptors, there is overwhelming evidence in the Art supporting that excitatory amino acid (EAA) receptors can induce selective neuronal death both, *in vitro* and *in vivo*. EAAs is one of the factors contributing to necrotic cell death that is due to ischemia, traumatic brain injury, hypoglycemia, and epileptic seizures, though it is unlikely that glutamate receptor activation is the major etiological factors in specific chronic neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration) (Boxer et al., 1997, Drug Discovery Today, p. 222, col. 1 paragraph 2). Application of EAA on neurons causes an increase in intracellular calcium. The mechanism by which "calcium overload" induces cell death has not been completely elucidated (Boxer et al., 1997, Drug Discovery Today, p. 222, col. 2 paragraph 2). Drug therapy that involved the use of blockers to the three classes of ionotropic receptors (e.g., linked to an ion channels) of EAA

(e.g., NMDA, AMPA, and Kainate receptors) and other therapies to reduce release of Ca^{++} from intracellular stores is an on going process providing conflicting treatment results (Boxer et al., 1997, p. 224, col. 1, last paragraph bridging to col. 2 paragraph 1).

In relation to intracellular targets, several intracellular targets for neuronal protection such as calpain inhibitors, blockage of nitric oxide (NO) and scavenge of reactive oxygen species have been considered in the Art. Calpain are proteases activated only by high levels of calcium and they target structural proteins. Boxer teaches (1997, p. 224, col. 2, last paragraph) that calpain inhibitors are perhaps the most attractive intracellular target for neuronal protection, however a mayor limitation of this type of strategy is that ‘once high levels of intracellular calcium have occurred, a variety of parallel pathways are activate’. Similarly, the blockage of NO, which has been shown to be cytotoxic and activated by elevated intracellular calcium, is not specific to the brain and also inhibits endothelial NO, which produces undesirable effects on systemic blood pressure and cerebral flow (Boxer, 1997, p. 225, col. 1, paragraph 2). Boxer discloses (1997, p. 225, col. 2, paragraph 2), oxidative damage as a mechanism contributing to etiology of chronic degenerative diseases, specifically in AD wherein overproduction of β -amyloid may kill neurons via generation of reactive oxygen species. Mitochondria dysfunction may also contribute to the pathogenesis of chronic neurodegenerative disorder by chronic poisoning of the oxidative phosphorylation pathway, decreasing production of ATP and ultimately producing pathologies seen in Huntington’s disease and parkinsonism. Thus antioxidants such as vitamin E, β -carotene and vitamin A may be potential as prophylactic prevention to relieve oxidative stress. Transforming growth factor- β 1 also protect neurons in culture against both calcium and free radical-mediated degeneration via preservation of

mitochondrial potential and function. Similarly, neurotropic factors (e.g., nerve growth factor, basic fibroblast, brain-derived neurotropic factor) attenuate glutamate-induced peroxides and increase antioxidant enzymes and thus protect cells from oxidative stress (Boxer, p. 226, col. 1, paragraph 1). However, factual data about specificities of neurotropic factors in adult CNS have not been well work out (Schwab, Science, 2002, Repairing the injured spinal cord, p. 1030, col. 2, paragraph 2). Schwab teaches that “ the regenerative effects of nerve growth factor on peripheral nerves, for example, have turned our to be clinically useless because nerve growth factor affects pain-sensitive neurons, resulting in hyperalgesia (increase sensitivity to pain). Although more that 30 neurotropic factors are known, fewer than six of them have been investigated as potential preventions for lesioned spinal cord in animal models”. Similar insight into the unpredictability for neuronal protection is provided by Boxer when he teaches that progressive degenerative diseases may all result form an inability of the brain to prevent free radical damage or oxidative stress (p. 226, col. 1, paragraph 1).

In so far as programmed cell death (PCD), an inappropriate activation of apoptosis may lead to pathologies related to stroke, Ad, AIDS dementia and aging (Boxer, p. 226, col. 2, paragraph 2). Recently, a cascade of events involved in activation of extracellular and intracellular pathways leading to cell death has disclosed a new family of proteases, caspases (Davis, 2001, Current Opinions in Investigational Drugs). Caspases are proteolytically activated from an inactive proenzyme or zymogen stage, by mechanisms that involved extrinsic and intrinsic cellular pathways regulating maturation of caspase 8 and caspase 9, respectively. Substrates for the effectors of caspases are plentiful, including many proteins associated with the pathology of neurodegenerative disorders (Davis, 2001, p. 655, col. 2), such as the protein

associated with Kennedy's disease, androgen receptor. Moreover, Davis teaches that "the precise mechanism by which the caspases cleavage of these substrates contributes to the cell process is not known, although several of these cleaved proteins have been shown to cause the death of cells and to increase the sensitivity of cells to other death stimuli" (p. 656, col. 1, paragraph 1). Davis anticipates that caspase cleavage of the holoprotein substrate might cause a loss of a protective function; indeed, some of the substrates have been reported to exhibit anti-apoptotic properties (Davis, 2001, p. 655, col. 2).

Hence, molecular mechanisms in neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease) more likely to mediated cell death process, appears to involved a highly regulated, pleiotropic cascade of events (Davis, Current Opinion in Investigational Drugs, p. 654, col. 2, last paragraph). As neuronal cell death is unlikely to have a single, discrete pathway, one skilled in the Art at the time of the invention could not reasonably predict the use of a method of administering nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease).

Insofar as the extrapolation of results from the murine model to the human model, prior Art teaches that the conditions of a particular disease in an animal model may not correspond with the human condition. For example, mice with mutations in the cystofibrosis gene do not exhibit the pulmonary effects of cystic fibrosis seen in man, but rather suffer from severe gastrointestinal obstruction (Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, December 7, 1995, p.11 paragraph. 3). Thus,

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the relevance of animal models for prevention of a human neurodegenerative diseases may be compromised by phenotypical difference between the human patient and animal models of the disease. Thus, the state of prior Art teaches a lack of nexus between murine model to the human model.

Hence, one skill in the Art at the time of the invention could not reasonably predict the use of any nonviral, nucleic acid molecule expressing a neuronal marker by any route of administration for prevention of neurodegenerative diseases. Further, a detailed study of the different non-viral gene transfer systems is required in relation to the systemic and intracellular barriers for expression of the therapeutic protein of interest. Brown et al., (2001) conclude that "It is unlikely that a gene delivery system will emerge which has universal applicability and the first license gene therapeutics will utilize a gene delivery system which has been tailored to give high levels of gene expression when administered to treat a specific disease".

The predictability or lack thereof in the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

Guidance in the Specification and working examples

Applicant contemplates in Examples [50] gene expression of genes shown in Figure 9, by comparing right to left eye in animals, and in Example [51] gene expression of genes shown in

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Figure 8. However, Applicant is silent about any factual data of any method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent neurodegenerative diseases.

Level of Skill in the Art

The relative skill of those in the art is considered to be relatively high at the time the invention was made.

Analysis of Quantity of Experimentation

In relation to the use of non-viral gene transfer technology for prevention of any human neuronal cell death, the Art of record teach that nonviral gene therapy involves complex issues and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies. Prior Art teaches the challenges faced in clinical applications of non-viral gene therapy and the need to use a gene delivery tailored as required by the clinical target. Part of the transient expression is attributed to the inability of naked DNA to successfully address the problem of endosomolytic destruction and nuclear entry into differentiated non-dividing or slowly dividing cells. While viral vectors have evolved specific mechanisms for release of viral DNA from endosomes, and mechanisms to gain entry across the nuclear pore complexes, the inability to overcome these limitations for successful nonviral gene transfer requires further developing and testing of the nonviral vectors. Hence, issues such as targeting, endosomolytic release, cytoplasmic stability and nuclear entry have to be addressed for a successful gene expression and prevention with nonviral therapy. With respect to the prevention of neuronal cell death, the art of record teaches the need for a better understanding of the pathology molecular mechanisms in neurodegenerative diseases (e.g., Alzheimer's disease,

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Parkinson's disease, age-related macular degeneration, Huntington's disease) since cell death process appears to involve a highly regulated, pleiotropic cascade of events. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of preventing a human disorder associated with neuronal cell death in the claims is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. Applicants disclose no other details in the as-filed specification in relation to a method a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule expressed in sufficient levels to prevent neuronal cell death. Hence, the scope of the patent protection sought by the Applicant as defined by the claim fails to correlate with the scope of enabling disclosure set forth in the specification.

With regard to the correlation of a murine model with a human gene therapy model, the Art does not recognize a nexus between the murine model, and the prevention of neural cell death. The working examples presented share no nexus with the attainment of clinically efficacious transgene levels. Moreover, it is unclear how by comparing the right and left eye of a rat of the elected species neuronal marker relates to prevention of neuronal cell death, the specification does not teach how to select or use any neuronal marker, nor does it disclose what properties of neuronal markers are desirable for use in the methods of the claimed invention. Hence, due to differences cellular environments between the *in vivo* eye expression in a murine model in comparison to the various cell types to which the protein encoded by the nucleic acid of the administered molecule expressing a neuronal is exposed to when it is administered into a human environment, there is no evidence that the behavior of the expressed gene in the *in vivo*

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murine model would be predictive of the behavior of the protein in a human model. Hence, one of skill in the art will not find it reasonably predictable how said *in vivo* murine model results could be extrapolated to a human environment without undue experimentation.

As such, and to the extent that the claimed invention is drawn to the methods of a method of preventing neuronal cell death in a mammal comprising administering to said mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease occasioned by neuronal cell death (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders, the as-filed application does not provide sufficient guidance and/or working examples for a skilled artisan to reasonably enable the claim invention.

Due to the large quantity of experimentation necessary to generate the infinite number of derivative as recite in claims 10 and dependent claims 12-19 and subsequent screening for selection of any methods a of preventing neuronal cell death by administering a nucleic acid molecule comprising a coding sequence for a neuronal marker, by any route, for the intended use of *in vivo* prevention any type of human disorder associated with neuronal cell death, one skilled in the Art will have to perform extensive experimentation with each of these parameters to find the embodiments embraced by Applicant's claims, and as such, this experimentation would be considered undue.

Conclusion

In conclusion, the disclosed information from the as-filed application plus the state of the prior art is not deemed sufficient to reasonably convey to one of ordinary skill in the art that the

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Specification is reasonably enabling for the full breadth of the claim at the time the invention was made, such is because the make and use of any method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease associated with neuronal cell death, the lack of proper animal models and therapeutic applications in human patients, insufficient guidance and direction in the specification, the inherent unpredictability in the Art, the state of the Art and the nature of the invention, one of ordinary skill in the Art to would be required to perform a large amount of experimentation to make and/or use the invention claimed by the Applicant

Hence, one skill in the Art at the time of the invention could not reasonably predict that a method of preventing neuronal cell death by administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule.

Conclusion

Claims 10 and dependent claims 12-19 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nguyen Dave can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

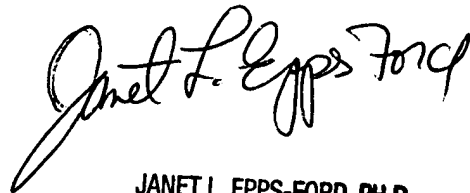
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A handwritten signature in black ink, reading "Janet L. Epps-Ford". The signature is written in a cursive, flowing style with a large initial "J" and "E".

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER